SGLT2 Inhibitors and Cardiovascular Risk: Lessons Learned From the EMPA-REG OUTCOME Study

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Although cardiovascular (CV) mortality is the principal cause of death in individuals with type 2 diabetes (T2DM), reduction of plasma glucose concentration has little effect on CV disease (CVD) risk. Thus, novel strategies to reduce CVD risk in T2DM patients are needed. The recently published BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study demonstrated that in T2DM patients with high CVD risk empagliflozin reduced the primary major adverse cardiac event end point (CV death, nonfatal myocardial infarction, nonfatal stroke) by 14%. This beneficial effect was driven by a 38% reduction in CV mortality with no significant decrease in nonfatal myocardial infarction or stroke. Empagliflozin also caused a 35% reduction in hospitalization for heart failure without affecting hospitalization for unstable angina. Although sodium–glucose cotransporter 2 inhibitors exert multiple metabolic benefits (decreases in HbA$_{1c}$, body weight, and blood pressure and an increase in HDL cholesterol), all of which could reduce CVD risk, it is unlikely that the reduction in CV mortality can be explained by empagliflozin's metabolic effects. More likely, hemodynamic effects, specifically reduced blood pressure and decreased extracellular volume, are responsible for the reduction in CV mortality and heart failure hospitalization. In this Perspective, we will discuss possible mechanisms for these beneficial effects of empagliflozin and their implications for the care of T2DM patients.

The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study (1) provided evidence that empagliflozin reduces cardiovascular (CV) mortality and heart failure in high-risk patients with type 2 diabetes (T2DM) with a previous CV event (myocardial infarction [MI], stroke, amputation, multivessel coronary artery disease, or coronary artery bypass graft). Although the results have important clinical implications for the care of T2DM patients, they raise a number of questions with regard to *1*) mechanism of action, *2*) generalizability, and *3*) class effect. In this Perspective, we discuss the results of the EMPA-REG OUTCOME study, their implications for the care of T2DM patients, and future directions.

CV RISK AND T2DM

T2DM individuals manifest a two- to threefold greater risk of CV events compared with counterparts without diabetes, and CV mortality is responsible for ~80% of the mortality (2). In T2DM patients without MI, risk of CV death is similar to individuals without diabetes with prior MI (2). Although hyperglycemia is the principal risk factor for microvascular complications, it is a weak risk factor for CV disease (CVD), and interventional studies focused on reducing plasma glucose in T2DM have only a

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minor effect to reduce CV risk (3–6). Furthermore, it takes many years to observe the CV benefit associated with improved glycemic control (7,8). Most T2DM individuals manifest moderate-to-severe insulin resistance, which is associated with multiple metabolic abnormalities, i.e., obesity, dyslipidemia, and hypertension, all of which are CV risk factors (9). This cluster of CV/metabolic disturbances is known as the insulin resistance (metabolic) syndrome and is the principal factor responsible for increased CV risk in T2DM (10). Furthermore, the molecular mechanisms responsible for insulin resistance directly contribute to the pathogenesis of atherosclerosis, independent of the associated metabolic abnormalities (10). Thus, obese individuals without diabetes with the insulin resistance syndrome manifest a similarly increased risk for CVD compared with T2DM patients (11), supporting the concept that hyperglycemia is not a major determinant for the development of CVD in T2DM. Consequently, lowering blood pressure and improving lipid profile have a greater effect to reduce CVD risk than lowering plasma glucose concentration in T2DM (12) (Fig. 1). Therefore, it is not surprising that antidiabetes agents, e.g., insulin (3,13), sulfonylureas (3), and dipeptidyl peptidase 4 inhibitors (14–16), that lower plasma glucose without affecting other metabolic abnormalities associated with the insulin resistance syndrome have little beneficial effect to lower CVD risk in T2DM, especially when these agents are started late in the natural history of T2DM and atherosclerosis (4–6) (Supplementary Table 1).
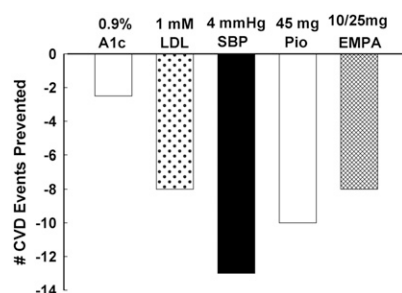

Figure 1—Number of CV events prevented in 200 T2DM patients over a period of 5 years in whom HbA$_{1c}$ was lowered by 0.9%, LDL cholesterol by 1 mmol/L, and systolic blood pressure by 4 mmHg and who were given 45 mg pioglitazone (Pio) or empagliflozin (EMPA) (10 or 25 mg per day) (1,11,17).

Conversely, pioglitazone, which improves insulin sensitivity (17) and multiple components of insulin resistance syndrome, i.e., blood pressure and lipids, exerts a favorable effect on CVD risk in T2DM individuals, independent of its glucose-lowering action (18). In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), pioglitazone lowered the main secondary end point (CV death, nonfatal MI, and stroke) by 16% ($P = 0.025$) (18).

METABOLIC EFFECTS OF SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITORS

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have a unique mechanism of action, which is independent of insulin secretion and insulin action (19). By inhibiting SGLT2 in the renal proximal tubule, they lower plasma glucose by producing glucosuria. This unique mechanism of action, in addition to lowering plasma glucose, corrects a number of metabolic and hemodynamic abnormalities that are risk factors for CVD (19). Urinary glucose loss produces negative caloric balance, resulting in a weight loss of 2–3 kg. Approximately two-thirds of the weight loss is fat, with subcutaneous and mesenteric fat loss contributing equally to the reduction in total body fat (20). SGLT2 inhibition decreases sodium reabsorption in the proximal tubule and exerts diuretic/natriuretic effects (21). SGLT2 inhibition also promotes urinary sodium excretion by causing osmotic diuresis. The result is a modest decrease in extracellular volume of ~5–10% (21). This natriuretic effect, combined with the more long-term reduction in body weight, contributes, in part, to decreases in systolic/diastolic blood pressure (4–5/1–2 mmHg), which is observed with all SGLT2 inhibitors (22). Blood pressure reduction is not accompanied by an increase in heart rate and is independent of background antihypertensive therapy (22), suggesting that SGLT2 inhibition might reduce sympathetic tone or influence other hormonal factors that contribute to decreased blood pressure without increasing heart rate. SGLT2 inhibitors cause a small increase in plasma LDL and HDL cholesterol and a decrease in plasma triglycerides (23); LDL/HDL cholesterol ratio remains unchanged. The mechanism by which SGLT2 inhibitors cause these changes in lipid profile remains unknown. Weight loss can explain, in part,

the decrease in triglycerides and increase in HDL cholesterol. The mechanism(s) responsible for increased LDL cholesterol and clinical significance of this increase requires further study.

T2DM individuals manifest moderate-to-severe insulin resistance (9). It has been suggested that insulin resistance per se contributes to the pathogenesis of atherosclerosis, independent of accompanying metabolic abnormalities (10), i.e., obesity, dyslipidemia, or hypertension. Thus, improving insulin sensitivity would be anticipated to reduce CV risk. We (24) and others (25) have demonstrated that SGLT2 inhibitors by alleviating glucotoxicity improve insulin sensitivity. Two weeks of dapagliflozin treatment improved whole-body insulin-mediated glucose uptake by 20–25%, measured with the euglycemic insulin clamp (24).

Because of the beneficial cardiometabolic/hemodynamic profile associated with SGLT2 inhibitor therapy, one might expect that this class of drugs would lower CVD risk in T2DM, independent of its glucose-lowering effect. Thus, the EMPA-REG OUTCOME study, which was required by U.S. Food and Drug Administration to establish CV safety, was powered not only for noninferiority compared to placebo but also for superiority.

THE EMPA-REG OUTCOME STUDY

The EMPA-REG OUTCOME study (1) is the first study to provide evidence that an antidiabetes agent decreases CV events. In 7,020 T2DM patients with established CVD, empagliflozin significantly reduced (hazard ratio [HR] 0.86 [95% CI 0.74–0.99], $P = 0.04$) the primary major adverse cardiac event (MACE) outcome (CV death, nonfatal MI, nonfatal stroke). However, several outcomes were surprising. First, the primary outcome was driven by decreased CV mortality and a striking disconnect between the three MACE components was observed: 1) for nonfatal MI, HR (0.87) decreased slightly but not significantly ($P = 0.22$); 2) for stroke, HR (1.24) increased slightly but not significantly ($P = 0.22$); and 3) for CV death, HR (0.62) decreased significantly by 38% ($P = 0.001$). Second, unlike other interventions that reduce CV risk, e.g., lowering LDL cholesterol (26) and blood pressure (27), separation between empagliflozin and placebo curves occurred very early, and reduction in the primary outcome

was evident 3 months after starting empagliflozin. Third, the beneficial effect of empagliflozin on mortality and hospitalization for heart failure widened progressively over the 3.1 years of treatment. Fourth, both empagliflozin doses (10 and 25 mg) had a similar effect on outcome measures with no dose-response relationship.

POSSIBLE MECHANISMS

Is It the Metabolic Actions of Empagliflozin?

Inhibition of renal SGLT2 in T2DM exerts multiple metabolic effects (e.g., reduced HbA$_{1c}$, weight loss, increase in fat oxidation, and increase in glucagon secretion) that can affect cardiac function and potentially influence CV mortality. Reduction in CV death without decrease in MI or stroke suggests that the beneficial effect of empagliflozin is to improve survival among patients experiencing a CV event rather than to slow the atherosclerotic process and prevent atherosclerotic events, i.e., MI and stroke. Reduction in CV death (5.9 to 3.6%, $P < 0.001$) was observed across all diagnostic categories (sudden death, 1.6 to 1.1%; worsening heart failure, 0.8 to 0.2%; acute MI, 0.5 to 0.3%; stroke, 0.5 to 0.3%; other CV death, 2.4 to 1.6%). The latter category includes deaths not explained by other known causes. The majority of such cases result from acute MI and arrhythmias, and this category is not as diagnostically sound as the others. Empagliflozin failed to reduce hospitalization from unstable angina (HR 0.97, $P = 0.97$). Because of 1) the lack of beneficial effect of empagliflozin on nonfatal stroke and nonfatal MI, 2) the absence of reduction in unstable angina, and 3) the rapidity of onset of decrease in CV mortality, it is highly unlikely that the decrease in MACE outcome in the EMPA-REG OUTCOME study results from slowing the atherosclerotic process by empagliflozin (Fig. 2).

Glycemic Control

It is unlikely that empagliflozin reduced mortality in the EMPA-REG OUTCOME study by improving glucose control. First, hyperglycemia is weak risk factor for CVD (12). Intensive glycemic control failed to decrease CV events in the UK Prospective Diabetes Study (UKPDS) (3), Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (4), Action in Diabetes and Vascular Disease: Preterax
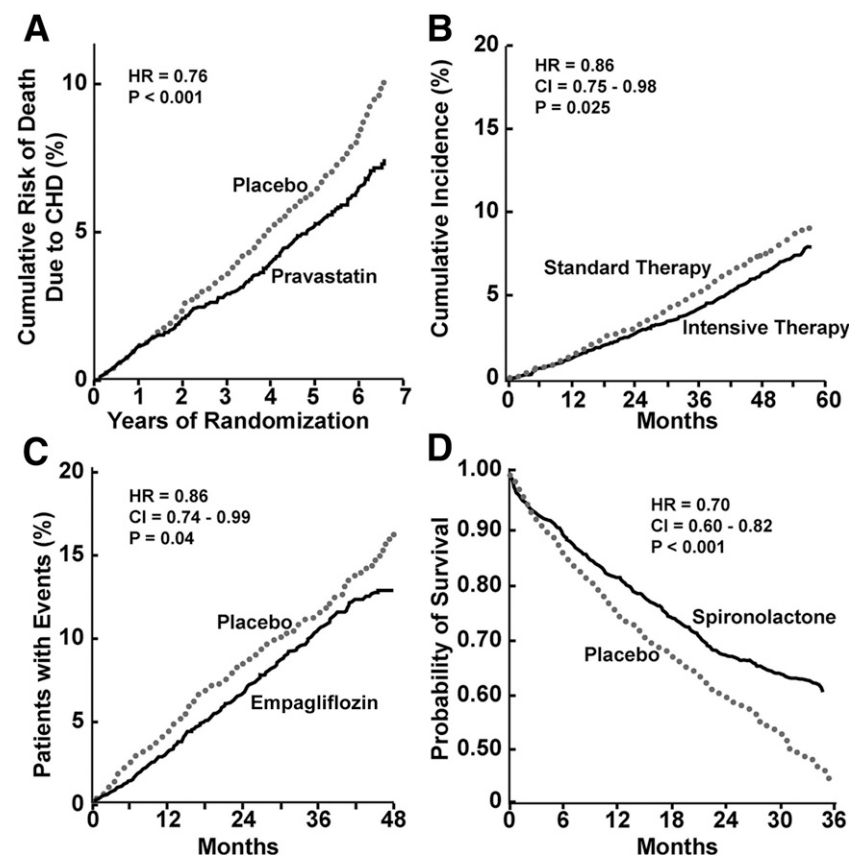

Figure 2—Kaplan-Meier plot of the effect of various interventions on CV outcome. A: Effect of pravastatin on CV events in the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study (29). B: Effect of lowering blood pressure on mortality in the ACCORD study (4). C: Effect of empagliflozin on CV events in the EMPA-REG OUTCOME study (1). D: Effect of spironolactone on mortality in patients with CHF (40).

and Diamicron MR Controlled Evaluation (ADVANCE) study (5), and Veterans Affairs Diabetes Trial (VADT) (6). Second, the difference in HbA$_{1c}$ between empagliflozin and placebo groups was modest: 0.45% at 90 weeks and 0.28% at 204 weeks. Third, it took ~10 years in UKPDS (7) and VADT (8) to demonstrate a small (~10%), though significant, reduction in CV events by tight glycemic control, while the effect of empagliflozin on CV mortality was evident at 3 months and well established at 6 months.

Shift in Fuel Metabolism

SGLT2 inhibitors shift whole-body metabolism from glucose to fat oxidation (24,25) (Fig. 3). Two and 4 weeks of treatment with dapagliflozin and empagliflozin, respectively, reduced the respiratory quotient (RQ) during fasting state, indicating a decrease in glucose oxidation and increase in fat oxidation. Dapagliflozin caused a 14% increase in fat oxidation and 20% reduction in glucose oxidation (24). During a mixed meal, glucose oxidation decreased

by 60% and fat oxidation increased by 20% after 4 weeks of empagliflozin. Because the amount of oxygen required to generate the same amount of ATP is greater with fat compared with glucose (28), the shift from glucose to fat oxidation would increase myocardial oxygen demand, and this would be expected to worsen myocardial ischemia in T2DM patients. Thus, increased myocardial fat oxidation caused by empagliflozin in the EMPA-REG OUTCOME study cannot explain the reduction in CV mortality caused by the drug.

Ketones

SGLT2 inhibitors cause a shift from glucose to fat oxidation and the end product of fatty acid oxidation is acetyl CoA, which either can enter the tricarboxylic acid cycle or be converted to ketones, the latter being favored by the SGLT2 inhibitor–induced stimulation of glucagon secretion (24,25) (Fig. 3). The rise in plasma ketone concentration is small (0.3–0.6 meq/L) (24,25). Like free fatty acids, the amount of oxygen required
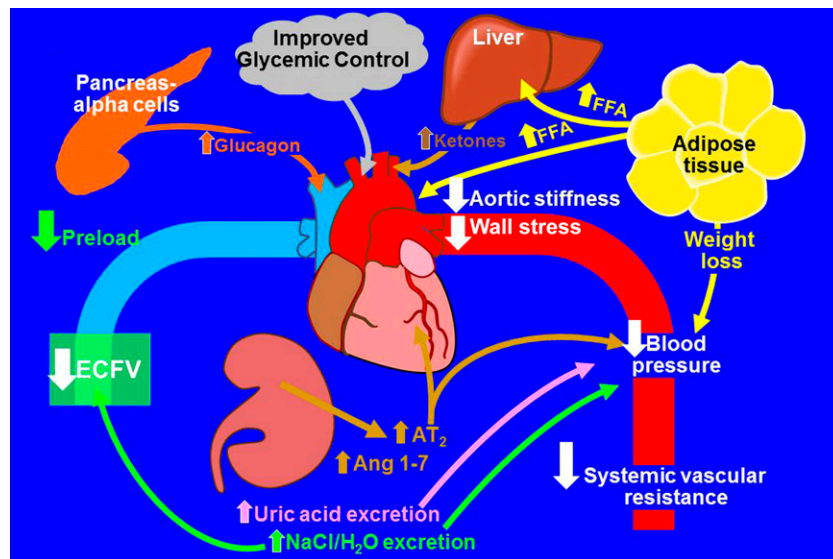
Figure 3—Schematic representation of the possible metabolic and hemodynamic mechanisms via which empagliflozin reduced mortality and hospitalization for heart failure in the EMPA-REG OUTCOME study. Because of the rapidity of onset of these beneficial effects and the known CV benefits of blood pressure and volume reduction from previous trials with antihypertensive agents and diuretics, it is likely that the hemodynamic and volume-depleting actions play a pivotal role in the cardioprotective effects of empagliflozin. It seems less likely that the metabolic/hormonal effects (shift from glucose to fat/ketone oxidation, reduced plasma uric acid concentration, weight loss, increased glucagon secretion, increased angiotensin [Ang] 1-7, and AT_2 receptor activation) of empagliflozin therapy could play a role in the drug's cardioprotective effects (see text for a more detailed explanation). ECFV, extracellular fluid volume.

to generate the same amount of ATP is greater with ketones compared with glucose. However, the heart avidly extracts and consumes ketone bodies and ketone body oxidation may improve cardiac muscle efficiency (reviewed in 29). Further studies will be required to examine whether the preferential oxidation of ketones by the heart (29) provides an energetic benefit to the failing myocardium.

Uric Acid
SGLT2 inhibitors promote uric acid excretion and reduce the plasma uric acid concentration by ~0.7% mg/dL (Fig. 3). Increased uric acid levels long have been associated with increased CVD (30), but a causal link remains controversial. However, accumulating evidence in both humans and animals indicates that elevated plasma uric acid levels can cause hypertension, vascular damage, and impaired renal function (reviewed in 31). Although unlikely to explain the early reduction in CV mortality, the potential benefits of uric acid reduction to reduce blood pressure and prevent vascular damage may play a role in the progressive late separation in the mortality curves between empagliflozin and placebo. The reduction in plasma uric acid concentration also may contribute to

the impressive slowing of diabetic nephropathy observed in the EMPA-REG OUTCOME study.

Glucagon
SGLT2 is expressed in pancreatic α-cells and plays an important role in regulating glucagon secretion (32). Dapagliflozin (24) and empagliflozin (25) cause a robust increase in plasma glucagon in T2DM patients (Fig. 3). In experimental animals, glucagon receptor activation exerts a detrimental effect on myocardial function (33), and glucagon infusion in humans has no effect on left ventricular (LV) function (34). Thus, it is unlikely that an increase in plasma glucagon contributed to reduced CV mortality or hospitalization for heart failure by empagliflozin.

Weight Loss
Glucosuria, produced by SGLT2 inhibitors, causes caloric loss and a decrease in body weight. In the EMPA-REG OUTCOME study, empagliflozin-treated subjects lost ~2 kg. Although possible, it is unlikely that this small amount of weight loss contributed to the reduction in CV mortality that was observed within 2–3 months after the start of empagliflozin.

Is It a Direct Effect of the Drug?
Although SGLT2 is not expressed in cardiac myocytes, SGLT1 is present in myocardial tissue. Therefore, partial SGLT1 inhibition by empagliflozin could affect cardiac function. However, half-maximal effective concentration for SGLT1 inhibition by empagliflozin is 8.3 μmol/L, which is ~2,600-fold greater than for SGLT2, and the peak plasma empagliflozin concentration following the administration of 10 and 25 mg/day doses is ~500 and ~800 nmol/L. Moreover, most of the circulating drug is bound to plasma proteins and free drug concentration is much lower. Therefore, the expected plasma-free empagliflozin concentration in the EMPA-REG OUTCOME study would be very low, and it is very unlikely that the low circulating free empagliflozin level could have any effect on SGLT1 function. Further, if SGLT1 were inhibited by empagliflozin, myocardial function would be expected to decline, not improve. Consistent with this, SGLT1 inhibition by phlorizin (dual SGLT1/2 inhibitor) in experimental animals exerts a detrimental effect on LV function (35). We are unaware of any study that demonstrates that empagliflozin has a direct beneficial effect on the heart, unrelated to an effect on the SGLT2/SGLT1 transporters, although such an effect cannot be excluded. In summary, direct myocardial effects by empagliflozin are unlikely to explain the beneficial effect of the drug on CV mortality.

Is It Change in Plasma Electrolyte Concentration and/or Distribution?
SGLT2 inhibition produces negative sodium balance in the first 2–3 days after starting the drug without a change in plasma sodium concentration. What remains to be established is whether sodium redistribution between the intra- and extracellular compartments may have occurred as a result of the natriuretic effect of the drug. In animal models of heart failure, an increase in intracellular sodium has been reported. Preclinical studies also have reported heart tissue remodeling after the administration of SGLT2 inhibitors in association with a marked reduction of interstitial fibrosis (36). The latter, however, requires time and is unlikely to explain the early deviation of curves for CV mortality and heart failure hospitalization.

A small increase in plasma potassium concentration has been observed with some SGLT2 inhibitors, and hyperkalemia can cause arrhythmias. However, this would increase, not decrease, CV mortality. No consistent changes in plasma chloride, bicarbonate, or calcium concentrations have been reported with SGLT2 inhibitors.

Small increases in serum phosphate (3–5%) and magnesium (7–9%) have been reported with SGLT2 inhibitors. It is unlikely that such a small increase in serum phosphate could affect myocardial function, and serum magnesium correlates poorly with tissue magnesium levels.

Is It the Blood Pressure?

Although most participants in the EMPA-REG OUTCOME study were hypertensive and >90% received antihypertensive therapy, starting blood pressure was well controlled (135/77 mmHg). The decrease in systolic/diastolic blood pressure in the EMPA-REG OUTCOME study was ~5/2 mmHg, and was maintained throughout the 3.1-year study duration. Such a decrease in blood pressure could contribute to the reduction in CV events in the EMPA-REG OUTCOME study. However, in studies that examined the effect of blood pressure reduction on CV events, the decrease became evident only after 1 year (27,37) (Fig. 2). Moreover, lowering blood pressure generally has a greater impact on stroke reduction than on other cardiac events (27,37). In the EMPA-REG OUTCOME study there was a small, albeit nonsignificant, increase in nonfatal stroke. Thus, it is unlikely that the decrease in CV events in empagliflozin-treated individuals can be explained solely by the decrease in brachial artery blood pressure. However, reduction in brachial artery blood pressure may underestimate central aortic pressure and provides no information about aortic stiffness, both of which are independent predictors of CV mortality and LV function (38,39). Results from the Conduit Artery Function Evaluation (CAFE) study (40) demonstrated that, despite similar brachial arterial blood pressures, subjects with hypertension and treated with amlodipine/perindopril had significantly lower central aortic blood pressure than the group treated with atenolol/thiazide. Further, reduction in central aortic blood pressure was strongly associated with reduced CV events in a post hoc analysis of 2,073 participants. If empagliflozin caused a greater decrease in central aortic pressure than evident by the decrease in brachial artery blood pressure and reduced aortic stiffness, it could have greater impact on cardiac events and heart failure than on stroke. Consistent with this hypothesis, empagliflozin has been shown to reduce aortic stiffness in subjects with diabetes, possibly by reducing oxidative stress or suppressing inflammation (41). Changes in nitric oxide and systemic renin-angiotensin-aldosterone system activity were unrelated to the decline in aortic stiffness following empagliflozin therapy (37). Further, the diuretic effect of empagliflozin and the accompanying decrease in intravascular volume could further decrease central aortic pressure and produce an afterload reduction effect that improves LV function, reduces cardiac workload, and decreases myocardial oxygen demand (Fig. 3). These hemodynamic effects of empagliflozin would be expected to reduce cardiac events, particularly in subjects with ischemic heart disease, impaired LV function, and congestive heart failure (CHF). Consistent with this scenario, participants with history of heart disease benefited most from empagliflozin treatment. The HR for 3-point MACE was 0.83 (95% CI 0.68–1.04) for patients with history of coronary heart disease only, 0.94 (0.47–1.88) for patients with peripheral vascular disease only, and 1.15 (0.74–1.78) for patients with stroke only. Thus, it is possible that these hemodynamic effects of empagliflozin contributed to its beneficial CV effect, particularly in subjects with reduced LV function and CHF. Unfortunately, no information on baseline LV function or change in LV function in response to therapy is available from the EMPA-REG OUTCOME study. Future studies examining the impact of SGLT2 inhibitors on central aortic and brachial artery blood pressure, aortic stiffness, and LV function will add insight about this hypothesis. Such hemodynamic effects of empagliflozin also could explain lack of relationship between empagliflozin dose and CV outcomes. As empagliflozin 10 mg produces near-maximal glucosuric, natriuretic, and blood pressure–lowering effects, the beneficial CV effect of 10 and 25 mg doses would be expected to be similar (42). Last, empagliflozin caused a 5/2 mmHg decrease in systolic/diastolic blood pressure without any increase in heart rate. This is consistent with the action of the drug to reduce sympathetic tone, which could have favorable effects on CV mortality. However, previous studies from our laboratory (24) suggest that the increase in endogenous (hepatic) glucose production observed with SGLT2 inhibitors is mediated by the stimulation of the renal sympathetic nerves. If this was associated with a generalized activation of the sympathetic nervous system, one would expect heart rate to increase, not decrease, as was observed in the EMPA-REG OUTCOME study. Further studies are needed to examine the effect of SGLT2 inhibitor therapy on the sympathetic nervous system.

Empagliflozin reduced hospitalization from CHF by 35%. Thus, it is possible that empagliflozin reduced CV mortality by improving survival specifically among patients with compromised LV function and/or clinically symptomatic CHF. A recent subanalysis showed that empagliflozin similarly reduced CV mortality in subjects with and without heart failure at time of entry into the EMPA-REG OUTCOME study. However, diagnosis of heart failure at baseline was based on self-reporting rather than on measured LV function. Further, subjects who did not report a history of heart failure and developed heart failure during the study were placed in the category without heart failure. Because the diagnosis of heart failure at baseline was based on self-reporting, it is possible—in fact likely—that many individuals who developed heart failure during the study actually had heart failure at baseline and, thus, were misclassified. Last, the reduction in CV mortality became evident shortly after starting therapy. This time course is reminiscent of the effect of spironolactone on survival in subjects with CHF (43) (Fig. 2). It is possible that the entire benefit of empagliflozin on CV mortality occurs secondary to the drug's unique action to simultaneously reduce both preload (reduction of plasma volume) and afterload (improved blood pressure and aortic stiffness) in patients with reduced LV function and heart failure (Fig. 3). Measurement of B-type natriuretic peptide could have added insight about this hypothesis and been helpful in identifying this high-risk population. Exploring this possibility not only would improve our understanding of the mechanism(s) by which empagliflozin reduces

CV mortality but also would identify a subgroup of patients with diabetes and existing heart failure who would benefit most from SGLT2 inhibitor treatment.

Reduction in the intravascular volume by empagliflozin could lead to activation of the renin-angiotensin-aldosterone system, leading to an exacerbation of the underlying CVD by stimulating the type 1 angiotensin (AT_1) receptor (44). However, 81% of patients with diabetes in the EMPA-REG OUTCOME study were receiving ACE inhibitors or angiotensin receptor blockers. This would favor activation of the AT_2 receptor and angiotensin 1-7 pathway, resulting in vasodilation; antiproliferation; antihypertrophy; antiarrhythmic, anti-inflammatory, positive inotropic effects; and reduction in microalbuminuria (45) (Fig. 3). Microalbuminuria is a known risk factor for CVD, although a direct causal association has yet to be established.

Does Empagliflozin Have an Effect to Slow Atherosclerosis?

Empagliflozin-treated subjects experienced ~2 kg weight loss, 2 mg/dL increase in HDL cholesterol, and 5 mmHg decrease in systolic blood pressure compared with placebo-treated subjects. These benefits would be expected to slow the atherosclerotic process and reduce nonfatal CV events. However, nonfatal CV events (MI and stroke) were not affected by empagliflozin. It is possible that the study duration was too short to observe the impact of these metabolic/hemodynamic effects on atherosclerosis-related events or that the antiatherosclerotic effect of empagliflozin may have been obscured by the advanced atherosclerotic condition of the participants. It is also possible that the increase in plasma LDL, although small, negated some beneficial effect of empagliflozin on CV risk factors. Last, there was an 11% and 7% increase in insulin and sulfonylurea use in the placebo group. These agents are associated with weight gain and adverse CV outcomes (8,46). It is possible that, in part, separation in MACE outcome curves between empagliflozin-treated and placebo-treated patients is explained by a detrimental impact of the hypoglycemic agents used in the placebo group.

Is There a Place for Combination Therapy With Pioglitazone?

Metformin long has been considered to exert some CV protection. Such an effect, however, is based primarily on a small group (*n* = 342) of obese T2DM patients in the UKPDS. Pioglitazone is the only other antidiabetes agent shown to lower CV events in T2DM (18). In the PROactive study, pioglitazone reduced the main secondary end point, MACE, by 16% (HR 0.84 [95% CI 0.72–0.98], *P* = 0.027), although the primary end point (MACE plus peripheral vascular disease) did not reach statistical significance due to an increase in the number of leg revascularizations. Of note, each component of the MACE end point decreased significantly with pioglitazone (death from 4.63 to 4.22%, MI from 4.48 to 4.00%, and stroke from 3.64 to 2.91%). Of particular note, recurrent stroke (HR 0.53, *P* = 0.008) and recurrent MI (HR 0.72, *P* = 0.045), which were not reduced in the EMPA-REG OUTCOME study, were markedly decreased in PROactive study (47,48). In addition, pioglitazone does not exert any negative effect on LV function and improves diastolic dysfunction (49), improves the lipid profile (17), reduces blood pressure (afterload) (50), improves endothelial dysfunction, and slows atherosclerosis (51–53). Thus, it is possible that combined pioglitazone/empagliflozin therapy would exert an additive, even synergistic, effect to reduce afterload and to improve CV events. One could argue that fluid retention with pioglitazone could offset some of the beneficial hemodynamic effects of empagliflozin. Fluid retention with pioglitazone is related to the drug's sodium retentive effect on the kidney; however, despite increased salt/water retention, pioglitazone significantly decreased systolic blood pressure (18,50). In the PROactive study, the incidence of "heart failure" in pioglitazone-treated subjects was increased; nonetheless, overall mortality and CV events in this group decreased compared with the placebo group, although the decrease was not as great as in pioglitazone-treated individuals who did not experience "heart failure" while on the thiazolidinedione (18). Thus, salt/water retention with pioglitazone does not negate the drug's beneficial CV effects in patients with heart failure. In a recent study involving 3,876 patients with a recent stroke or

transient ischemic attack, pioglitazone reduced the primary outcome of fatal or nonfatal stroke and MI by 26% (*P* < 0.001) (54). Of note, there was no increase in the incidence of heart failure in pioglitazone-treated individuals in this high-risk population in this study (54). Given the natriuretic effect of SGLT2 inhibitors, one might expect minimal fluid retention with combined pioglitazone/SGLT2 inhibitor therapy, especially if low pioglitazone doses (15–30 mg/day) are used.

Is It a Class Effect?

There are no significant differences in glucose lowering, body weight loss, and blood pressure reduction among the individual SGLT2 inhibitors. Using the Archimedes model, it has been predicted that, over a period of 20 years, patients with diabetes treated with dapagliflozin would experience a relative reduction of MI, stroke, CV death, and all-cause death (55). However, only well-designed CV intervention trials will provide a true answer to the question. The CANagliflozin cardioVascular Assessment Study (CANVAS) and DECLARE study, which examine the effect of canagliflozin and dapagliflozin, respectively, on CV outcomes, may help clarify whether the effect of empagliflozin to reduce CV events is a class effect or represents a specific pharmacological effect of empagliflozin. It is impossible at this time to determine whether other SGLT2 inhibitors will exert similar reductions in CV death and CHF hospitalization. Populations with diabetes in CANVAS and DECLARE differ significantly from those in the EMPA-REG OUTCOME study. Approximately 60–70% of patients in CANVAS and ~40% in DECLARE had a prior CV event and the remaining participants qualified based on CV risk factor profile. Moreover, the sample size (4,339 patients) in CANVAS (56) is relatively small compared with the EMPA-REG OUTCOME study. As the beneficial CV effects of empagliflozin most likely are mediated via its hemodynamic/volume depletion actions, one might expect other members of this class to have similar beneficial effects on CV events. However, because of different selection criteria in CANVAS and DECLARE, it is possible that a beneficial effect of canagliflozin and dapagliflozin to reduce CV mortality and CHF

Table 1—Possible mechanisms that could contribute to the reduction of CV mortality by empagliflozin in the EMPA-REG OUTCOME study

Effect	Likelihood	Reason
Metabolic actions		
Lowered plasma glucose concentration	Unlikely	Hyperglycemia is a weak CV risk factor; benefit of HbA_{1c} reduction on CVD takes ~10 years to observe
Increased fax oxidation	Unlikely	Increased oxygen demand per ATP generated
Increased plasma ketone concentration	Unlikely	Increased oxygen demand per ATP generated
Increased plasma uric acid concentration	Unlikely	Causal association with CVD not established
Increased plasma glucagon concentration	Unlikely	Physiological increase in glucagon has no effect on CV function
Weight loss	Unlikely	Weight loss is modest but may contribute to long-term reduction in blood pressure
Change in plasma electrolyte concentration	Unlikely	No consistent changes observed
Hemodynamic actions		
Decrease in blood pressure	Likely	Rapid reduction in blood pressure correlates with early CV benefit; proven CV protection in prior studies
Diuretic effect and decrease in extracellular fluid volume	Likely	Rapid reduction in extracellular fluid volume correlates with early CV benefit; proven protection against CHF in prior studies
Impaired arterial elasticity	Possible	Arterial stiffness is a CV risk factor; empagliflozin reduces arterial stiffness
Direct effect on the myocardium	Unlikely	No evidence
Decreased sympathetic tone	Possible	No increase in heart rate despite decrease in blood pressure and extracellular fluid volume

may not be observed even though the beneficial hemodynamic (and metabolic) effects of all three SGLT2 inhibitors are similar.

WHAT IS THE IMPACT OF THE EMPA-REG OUTCOME STUDY ON PATIENT CARE?

The EMPA-REG OUTCOME study results demonstrate that the addition of empagliflozin to the antidiabetes treatment regimen in high-risk T2DM patients with established CVD reduces CV mortality by 38%. We believe that such a dramatic effect on CV mortality justifies inclusion of empagliflozin in treatment regimen of T2DM patients with similar clinical characteristics to those in the EMPA-REG OUTCOME study, i.e., with established CVD. If such a high-risk T2DM patient is on another SGLT2 inhibitor, evidence-based medicine dictates a switch to empagliflozin. In T2DM patients who are earlier in the natural history of the disease and do not have well-established CVD, there are no data to support the use of one SGLT2 inhibitor over another. Currently, there are no data that any of the three SGLT2 inhibitors approved in the U.S. will have a CV protective effect in this T2DM population without clinically evident CVD. Therefore, the physician should feel comfortable using any of the three SGLT2 inhibitors in patients with diabetes without advanced cardiac disease. All three SGLT2 inhibitors

similarly reduce HbA_{1c}, blood pressure, and body weight and have a good safety profile.

WHAT IS NEXT?

As the results of the EMPA-REG OUTCOME study suggest that the beneficial effect of empagliflozin to lower CV mortality in T2DM patients most likely results from its hemodynamic rather than its metabolic effects, it is intriguing to examine the impact of the drug specifically in subjects with and without diabetes with reduced LV function (e.g., post-MI) and in subjects with existing CHF (Table 1). We postulate that the beneficial effect of empagliflozin on CV mortality and CHF hospitalization in these patient populations is likely to be quite robust. Additional studies to examine this possibility are indicated.

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